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**COMMENTARY**

# Recalibration of the HAS-BLED score – should haemorrhagic stroke account for 1 or 2 points?

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**Disclosures**

Professor Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer and Boehringer Ingelheim, and has been on the speaker bureaus for Bayer, BMS/Pfizer, Boehringer Ingelheim and Sanofi. Associate Professor Larsen has served as an investigator for Janssen Scientific Affairs, LLC and Boehringer Ingelheim, and has been on the speaker bureaus for Bayer, BMS/Pfizer, Roche Diagnostics, Boehringer Ingelheim and Takeda Pharma. Other authors – none declared

**Abstract**

Following a haemorrhagic stroke, it is uncertain whether this event scores 1 point (either for Stroke or Bleeding) or 2 points (1 point each for Stroke and Bleeding) on the HAS-BLED score. We investigated the value of a recalibration of the HAS-BLED score to account for 2 points from a haemorrhagic stroke.

We analysed data from the Danish nationwide cohort of incident atrial fibrillation (AF) patients from January 1999 to December 2013. The primary outcome in this observational study was major bleeding. The original- and the recalibrated HAS-BLED scores were assessed and event rates of major bleeding were calculated. We compared the predictive accuracy of major bleeding by C-statistics, the Net Reclassification Index (NRI) and Integrated Discrimination Improvement (IDI).

In a total of 210,299 AF patients, we observed an event rate for major bleeding of 4.3 per 100 person-years. The C-statistics for the two scores were modest: 0.613 (95%CI, 0.607-0.619) for the original and 0.616 (95%CI, 0.610-0.622) for the recalibrated. The NRI was 10.0% (95%CI 7.6%-12.4%). When assessing the NRI in less than 6 months follow-up, we observed a markedly higher NRI of 34.2%. The relative IDI was 23.6% (95%CI, 15.7%-31.5%) reflecting that the recalibrated HAS-BLED score more accurately predicted bleeding events.

Recalibration of the “S” component in the HAS-BLED score, counting 2 points for a haemorrhagic stroke, resulted in an increase in the C-statistics, NRI and IDI. This approach could potentially aid physicians in a more accurate bleeding risk assessment in AF patients.

## Introduction

Oral anticoagulant (OAC) treatment substantially reduces the risk of stroke and all-cause mortality in atrial fibrillation (AF) patients.[1] However, the decision to treat these patients relies on the expected risk of stroke weighed against the expected risk of bleeding. Contemporary guideline recommendations on OAC treatment are based on the $CHA_2DS_2$-VASc score (assessing the risk of thromboembolism) to initiate treatment or not.[2,3] The European Society of Cardiology further recommends formal assessment of the bleeding risk by the HAS-BLED score.[4] The HAS-BLED score summarizes to a maximum of 9 points (hypertension, abnormal renal/liver function [1 or 2 points], stroke, bleeding history or predisposition, labile INR, elderly [>65], drugs/alcohol concomitantly [1 or 2 points]).[5] A stroke currently contributes 1 point, and prior major bleeding (or its predisposition) contributes 1 point. Accurate bleeding risk assessment and optimal treatment guidance is pivotal in this frail population of AF patients who sustain an intracranial bleeding, especially given the strong associations to disability and mortality. [6,7]

Following a haemorrhagic stroke, it is it is unclear whether it should count 1 point (either for Stroke or Bleeding) or 2 points (1 point each for Stroke and Bleeding) on the HAS-BLED score. We investigated the value of a recalibration of the HAS-BLED score to account for 2 points from a haemorrhagic stroke.

**Methods and materials**

We used data from three Danish nationwide registries to conduct an observational cohort study investigating the original HAS-BLED score and the recalibrated HAS-BLED score. As previously done, we identified nonvalvular AF patients discharged from hospital from January 1st 1999 to December 31st 2013, and excluded patients who encountered a thromboembolism or major bleeding within 7 days after discharged.[8] The primary endpoint was major bleeding defined as a composite of intracranial bleeding (including traumatic intracranial bleeding events), gastrointestinal bleeding, acute anemia, bleeding from the urinary tract, and airway bleeding; see supplemental e-Table 1 for ICD-10 codes. Both primary and secondary diagnoses were included, but emergency room diagnoses were not included due to low validity. [9] We followed the patients from 7 days after hospital discharge and up to one year later or to occurrence of death, a major bleeding event, or end-of-study period, whichever came first.

We calculated two different HAS-BLED scores (original and recalibrated) at hospital discharge; only patients with a haemorrhagic stroke (non-traumatic intracranial bleeds) were reclassified in the recalibrated HAS-BLED score. Crude event rates (total number of events divided by accrued person-time) stratified by score ranging from 0-8 were reported. We did not have information on INR values; hence the "L" component was excluded from the calculations. To compare the predictive power of the scores we calculated and compared the (Harrell's) C-statistics.[10] We obtained estimates of bleeding risk in a competing risk of death setting, by using information directly from the cumulative incidence function.[11] Use of competing risk analyses are advised - especially in an elderly and fragile population - to obtain adequate risk estimates, which are not biased due to the competing risk.[12] To further compare the individual level changes in risk assessment from the two scores, we calculated a Net Reclassification Index (NRI), also in a competing risk setting.[13,14] In short, the NRI evaluates the proportion of patients with a

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We performed three sensitivity analyses, as follows: 1) stratifying patients according to baseline OAC treatment or initiation within the first 7 days after baseline. This was done in an attempt to indirectly assess if the missing "L" component from the data could influence the results (recognizing that patients not treated with OAC would not contribute to this component); 2) restricting the follow-up time to 6 months to assess performance of the recalibrated HAS-BLED compared to the original HAS-BLED in (relatively) short follow-up time. The motivation for this analysis was established by conceding an intracranial haemorrhage can be associated with increased event rates of recurrent major bleeding (including recurrent intracranial bleeding)[16]; and 3), we restricted the study period to the five most recent calendar years (2009-2013). Given the increasing availability of imaging technologies (MRI/CT scans) in this period, the validity of haemorrhagic stroke and/or haemorrhagic bleedings diagnosis were deemed to increase; hence, the proportion of reclassified patients (based on haemorrhagic stroke) would be more accurate.

**Results**

The study population comprised 210,299 AF patients (5,898 patients were excluded due to a thromboembolic/bleeding event within 7 days after discharge) with a median age of 74 [IQR: 65-82] and 46.6% were women. During one year of follow-up we observed 7,602 (3.62%) bleeding events. The mean HAS-BLED scores were 2.13 for the original score and 2.14 for the recalibrated score. The overall crude event rate of the primary endpoint was 4.3 per 100 person-years; Table 1 shows the event rates stratified according to points for the two scores. A total of 1,479 patients were reclassified in the recalibrated HAS-BLED score based on having sustained a haemorrhagic stroke when the observation time commenced. The predictive accuracy of the two scores in terms of the C-statistics was moderate, 0.613 (95%CI, 0.607-0.619) for the original and 0.616 (95%CI, 0.610-0.622) for the recalibrated HAS-BLED score, respectively. The NRI was 10.0% (95%CI, 7.6%-12.4%) displaying a significant improvement of correct classification by the recalibrated HAS-BLED scored compared to the original score. The relative IDI was 23.6% (95%CI, 15.7%-31.5%) reflecting that the recalibrated HAS-BLED score more accurately predicted bleeding events.

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**Discussion**

In this nationwide cohort study reflecting clinical practice, we recalibrated the original HAS-BLED score to account for 2 points if the stroke type was a haemorrhagic stroke. We observed an improved accuracy of the recalibrated HAS-BLED score as displayed by an improved NRI of 10.0% and a relative IDI of 23%.

Although the recalibration only resulted in a modest increase in the C-statistics, the potential of improved accuracy could be higher, as we only reclassified a very small proportion of this large cohort: of 2,218 patients who sustained an ICH event, we reclassified 1,479 (0.7% of total study population). The remaining 739 patients who were not reclassified all had prior events of ischemic stroke/TIA and a major bleeding event (or anaemia).

The recalibrated HAS-BLED score could potentially be more complicated to count than the original score. The physician who is presented with a patient who has sustain an haemorrhagic stroke has to take into account if this patient already has 1 point attributing prior bleeding and prior stroke. On the other hand, counting a haemorrhagic stroke as two points (1 for stroke and 1 for bleeding) appears intuitively applicable given the nature of the outcome. Importantly, the recalibrated score performs best within short follow-up time in terms of NRI, which could be related to the patients who were actually reclassified (those with a haemorrhagic stroke); however, this could represent the early excess risk associated with such 'high risk' patients.

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however risk assessment in AF patients is a continuum and risk (both for bleeding and thromboembolic events) does not remain static in these patients.

In conclusion, recalibration of the HAS-BLED score, counting 2 points for a haemorrhagic stroke, resulted in an improved accuracy of predicting major bleeding events. This approach could potentially aid physicians in a more accurate bleeding risk assessment in AF patients.

**References**


1. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146(12):857–67.

2. Camm AJ, Lip GYH, Caterina R De, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation - Developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;14(10):1385–413.

3. January CT, Wann FLS, Joseph F, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary. *J Am Coll Cardiol* 2014;64(21):2246–2280.

4. Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31(19):2369–429.

5. Pisters R, Lane DA, Nieuwlaat R, Vos CB de, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138(5):1093–100.

6. Marsh EB, Gottesman RF. Brain hemorrhage: restarting anticoagulation after intracranial hemorrhage. *Nat Rev Neurol* 2011;7(3):130–2.

7. Nielsen PB, Larsen TB, Skjoth F, Gorst-Rasmussen A, Rasmussen LH, Lip GYH. Restarting Anticoagulant Treatment After Intracranial Haemorrhage in Patients With Atrial Fibrillation and the Impact on Recurrent Stroke, Mortality and Bleeding: A Nationwide Cohort Study. *Circulation* 2015;In press. DOI 10.1161/CIRCULATIONAHA.115.015735

8. Lip GYH, Nielsen PB, Skjøth F, Lane DA, Rasmussen LH, Larsen TB. The value of the European society of cardiology guidelines for refining stroke risk stratification in patients with atrial fibrillation categorized as low risk using the anticoagulation and risk factors in atrial fibrillation stroke score: a nationwide co. *Chest* 2014;146(5):1337–46.

9. Johnsen SP, Overvad K, Sørensen HT, Tjønneland A, Husted SE. Predictive value of stroke and transient ischemic attack discharge diagnoses in The Danish National Registry of Patients. *J Clin Epidemiol* 2002;55(6):602–7.

10. Newson R. Comparing the predictive powers of survival models using Harrell's C or Somers' D. *Stata J* 2010;10(3):339–358.

11. Wolbers M, Koller MT, Witteman JCM, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. *Epidemiology* 2009;20(4):555–561.

12. Koller MT, Schaer B, Wolbers M, Sticherling C, Bucher HC, Osswald S. Death without prior appropriate implantable cardioverter-defibrillator therapy: A competing risk study. *Circulation* 2008;117(15):1918–1926.

13. Pencina MJ, D'Agostino RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med* 2011;30(1):11–21.

14. Klein JP, Andersen PK. Regression modeling of competing risks data based on pseudovalues of the cumulative incidence function. *Biometrics* 2005;61(1):223–229.

15. Pencina MJ, D'Agostino RB, Vasan RS. Statistical methods for assessment of added usefulness of new biomarkers. Clin. Chem. Lab. Med. 2010;48(12):1703–1711.

16. Aguilar MI, Hart RG, Kase CS, et al. Treatment of warfarin-associated intracerebral hemorrhage: literature review and expert opinion. *Mayo Clin Proc* 2007;82(1):82–92.

**Table 1:** Major bleeding event rates per 100 person-years for major bleeding events according to HAS-BLED scores for 1-year follow-up in incident atrial fibrillation patients.

| | Original HASBLED | | | Recalibrated HASBLED | | |
|---|---|---|---|---|---|---|
| Points | Person-time | Events | Event rate | Person-time | Events | Event rate |
| 0 | 19611 | 193 | 0.98 | 19611 | 193 | .98 |
| 1 | 41864 | 1127 | 2.69 | 41799 | 1,111 | 2.69 |
| 2 | 51933 | 2179 | 4.20 | 51703 | 2,149 | 4.16 |
| 3 | 43769 | 2392 | 5.46 | 43646 | 2,368 | 5.43 |
| 4 | 17359 | 1294 | 7.45 | 17472 | 1,316 | 7.53 |
| 5 | 3692 | 361 | 9.78 | 3965 | 402 | 10.14 |
| 6 | 425 | 52 | 12.25 | 456 | 59 | 12.94 |
| 7 | 22 | 4 | 18.23 | 23 | 4 | 17.36 |
| 8 | 12 | 0 | - | 22 | 0 | - |
| 9 (Labile INR) | NA | NA | NA | NA | NA | NA |
| Any score | 178676 | 7602 | 4.3 | - | - | - |
| Categorised risk | | | | | | |
| 0-2 (low risk) | 113408 | 3499 | 3.09 | 113113 | 3453 | 3.05 |
| ≥3 (High risk) | 65268 | 4103 | 6.29 | 65563 | 4149 | 6.33 |

Observation time starts after a quarantine period of 7 days relative to AF discharge.

**List of abbreviations:**

OAC: Oral anticoagulant

AF: Atrial fibrillation

ICD-10: International classification of disease version 10

INR: International normalized ratio

NRI: Net reclassification index

IDI: Integrated discrimination improvement

CI: Confidence interval

IQR: Interquartile range

TIA: Transient ischemic attack



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**Running title:** Recalibration of the HAS-BLED score

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**Abstract**

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In conclusion, recalibration of the HAS-BLED score, counting 2 points for a haemorrhagic stroke, resulted in an improved accuracy of predicting major bleeding events. This approach could potentially aid physicians in a more accurate bleeding risk assessment in AF patients.

## References


1. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146(12):857–67.

2. Camm AJ, Lip GYH, Caterina R De, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation - Developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;14(10):1385–413.

3. January CT, Wann FLS, Joseph F, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary. *J Am Coll Cardiol* 2014;64(21):2246–2280.

4. Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31(19):2369–429.

5. Pisters R, Lane DA, Nieuwlaat R, Vos CB de, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138(5):1093–100.

6. Marsh EB, Gottesman RF. Brain hemorrhage: restarting anticoagulation after intracranial hemorrhage. *Nat Rev Neurol* 2011;7(3):130–2.

7. Nielsen PB, Larsen TB, Skjoth F, Gorst-Rasmussen A, Rasmussen LH, Lip GYH. Restarting Anticoagulant Treatment After Intracranial Haemorrhage in Patients With Atrial Fibrillation and the Impact on Recurrent Stroke, Mortality and Bleeding: A Nationwide Cohort Study. *Circulation* 2015;In press. DOI 10.1161/CIRCULATIONAHA.115.015735

8. Lip GYH, Nielsen PB, Skjøth F, Lane DA, Rasmussen LH, Larsen TB. The value of the European society of cardiology guidelines for refining stroke risk stratification in patients with atrial fibrillation categorized as low risk using the anticoagulation and risk factors in atrial fibrillation stroke score: a nationwide co. *Chest* 2014;146(5):1337–46.

9. Johnsen SP, Overvad K, Sørensen HT, Tjønneland A, Husted SE. Predictive value of stroke and transient ischemic attack discharge diagnoses in The Danish National Registry of Patients. *J Clin Epidemiol* 2002;55(6):602–7.

10. Newson R. Comparing the predictive powers of survival models using Harrell's C or Somers' D. *Stata J* 2010;10(3):339–358.

11. Wolbers M, Koller MT, Witteman JCM, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. *Epidemiology* 2009;20(4):555–561.

12. Koller MT, Schaer B, Wolbers M, Sticherling C, Bucher HC, Osswald S. Death without prior appropriate implantable cardioverter-defibrillator therapy: A competing risk study. *Circulation* 2008;117(15):1918–1926.

13. Pencina MJ, D'Agostino RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med* 2011;30(1):11–21.

14. Klein JP, Andersen PK. Regression modeling of competing risks data based on pseudovalues of the cumulative incidence function. *Biometrics* 2005;61(1):223–229.

15. Pencina MJ, D'Agostino RB, Vasan RS. Statistical methods for assessment of added usefulness of new biomarkers. Clin. Chem. Lab. Med. 2010;48(12):1703–1711.

16. Aguilar MI, Hart RG, Kase CS, et al. Treatment of warfarin-associated intracerebral hemorrhage: literature review and expert opinion. *Mayo Clin Proc* 2007;82(1):82–92.

**Table 1:** Major bleeding event rates per 100 person-years for major bleeding events according to HAS-BLED scores for 1-year follow-up in incident atrial fibrillation patients.

| | Original HASBLED | | | Recalibrated HASBLED | | |
|---|---|---|---|---|---|---|
| Points | Person-time | Events | Event rate | Person-time | Events | Event rate |
| 0 | 19611 | 193 | 0.98 | 19611 | 193 | .98 |
| 1 | 41864 | 1127 | 2.69 | 41799 | 1,111 | 2.69 |
| 2 | 51933 | 2179 | 4.20 | 51703 | 2,149 | 4.16 |
| 3 | 43769 | 2392 | 5.46 | 43646 | 2,368 | 5.43 |
| 4 | 17359 | 1294 | 7.45 | 17472 | 1,316 | 7.53 |
| 5 | 3692 | 361 | 9.78 | 3965 | 402 | 10.14 |
| 6 | 425 | 52 | 12.25 | 456 | 59 | 12.94 |
| 7 | 22 | 4 | 18.23 | 23 | 4 | 17.36 |
| 8 | 12 | 0 | - | 22 | 0 | - |
| 9 (Labile INR) | NA | NA | NA | NA | NA | NA |
| Any score | 178676 | 7602 | 4.3 | - | - | - |
| Categorised risk | | | | | | |
| 0-2 (low risk) | 113408 | 3499 | 3.09 | 113113 | 3453 | 3.05 |
| ≥3 (High risk) | 65268 | 4103 | 6.29 | 65563 | 4149 | 6.33 |

Observation time starts after a quarantine period of 7 days relative to AF discharge.

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**e-Table 1:** ICD codes and ATC codes used in the study.

| | International Classification of Diseases 10th revision (ICD-10) code | Anatomical Therapeutic Chemical (ATC) code |
|---|---|---|
| **Condition** | | |
| Hypertension | | See specified definition* |
| Diabetes mellitus | E10.0; E10.1; E10.9; E11.0; E11.1; E11.9 | A10 |
| Ischemic stroke | I63; I64 | |
| Transient ischemic disease | G45 | |
| Abnormal renal function | I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61 | |
| Abnormal hepatic function | B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85 | |
| Prior Bleeding | I60-I62; D62; J94.2; H11.3; H35.6; H43.1; N02; N95; R04; R31; R58; K25.0; K26.0; K27.0; K28.0; K29.0; S06.3C; S06.4; S06.5; S06.6 | |
| Alcohol intake | E22.4; E52.9A; F10; G31.2; G62.1; G72.1; I42.6; K29.2; K70; K86.0; L27.8A; O35.4M; T51; Z71.4; Z72.1 | |
| Atrial fibrillation | I48 | |
| Major bleeding | D62 J942 H113 H356 H431 N02 N95 R04 R31 R58 | |
| Gastrointestinal bleeding | K250 K260 K270 K280 K290 | |
| Intracranial bleeding | I60 I61 I62 | |
| Traumatic intracranial bleeding | S063C S064 S065 S066 | |
| Retinal bleeding | H356 | |
| **Medication** | | |
| Aspirin | | B01AC06 |
| Non-steroidal anti-inflammatory drugs | | M01A |

* We identified subjects with hypertension from combination treatment with at least two of the following classes of antihypertensive Drugs:
I. Alpha adrenergic blockers (C02A, C02B, C02C)
II. Non-loop diuretics (C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52)
III. Vasodilators (C02DB, C02DD, C02DG, C04, C05)
IV. Beta blockers (C07)
V. Calcium channel blockers (C07F, C08, C09BB, C09DB)
VI. Renin-angiotensin system inhibitors (C09).

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